REMARKS

The specification has been amended to correct a typographical error in the pagination of a reference.

Claims 73-117 are pending in the application. Support for these new claims is found in the specification, as follows.

The phrase "so as to allow chain extension," is found in claims 73, 78, 84, 89 and 98; and "extendible by a polymerase," is found in claim 104. Similarly, "tagged primer...has been extended by a polymerase," is found in claims 76 and 82; "tagged primer...extended in length," is found in claim 92; "tagged first portion has been extended," is found in claim 98; and "extending the tagged oligonucleotide fragment," found in claim 101.

Support for methods involving the extension of a primer or oligonucleotide fragment is found, for example on page 9 at lines 18-19 ("They [the primers] must have a free 3' hydroxyl group to allow chain extension by the polymerase") and lines 22-24 ("The chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase"). Additional support is found on page 10 at lines 6-9 ("In turn, each tagged primer is then paired with one of the dideoxynucleotides and used in the primed synthesis reaction...") Extension may also be achieved by ligation, as described on page 11 at lines 14-28 and in Figure 1.

Attachment of the tag to a primer or oligonucleotide fragment through an amine linkage, as in claims 74, 80, 85, 90,93, 96, 99, 102 and 106 is described in the specification on page 11 at lines 2-6, as follows:

> The strategy used is to introduce an aliphatic amino group at the 5' terminus as the last addition in the synthesis of the oligonucleotide primer. This reactive amino group may then readily be coupled with a wide variety of amino reactive fluorophores or chromophores.

In addition, Examples III and IV (page 16, line 21 through page 20, line 24) provide experimental protocols for addition of an amino-modified phosphoramidite to an oligonucleotide and conjugation of dye molecules to the amino-modified oligonucleotide.

Attachment of a chromophore or fluorophore at or in the vicinity of the 5' end of a primer or oligonucleotide is recited in claims 91, 94, 97, 100, 103, and 107. Support is found in the specification on page 11 at lines 2-6 (quoted above) and on page 16, line 21 through page 20, line 24, where experimental protocols for addition of an amino-modified phosphoramidite to an oligonucleotide and conjugation of dye molecules to the amino-modified oligonucleotide are provided. Addition of the tag to the 5' end of a DNA molecule by ligation is described on page 11 at lines 14-28 and in Figure 1.

Claims 75, 76, 81, 82, 92, 98 and 101 recite primers, oligonucleotides, oligonucleotide fragments, or portions of oligonucleotides that have been base-paired or hybridized to a template or a complementary sequence. Support is found in the specification on page 9 at lines 19-20 ("They [the primers] must be complementary to a unique region...") and at lines 22-24 ("The chromophore or fluorophore must not interfere with the hybridization..."). Support is also found on page 10 at lines 26-28: "The dye conjugated primers retain their ability to specifically hybridize to DNA...." Additional support is found on page 20, line 28 through page 21, line 18, particularly page 21 at lines 8-10 ("...the derivatized primers retain their ability to hybridize specifically to the complementary strand.") and lines 16-18 ("...the strength of hybridization is not significantly perturbed by the presence of the dye molecules.").

Claims 77, 83, 95 and 105 are directed to extended primers or oligonucleotides, that have been separated from a template or a complementary sequence after extension. Support in the specification is found on page 11 at lines 30-34, where applicants state that the sequencing reactions are performed in the standard fashion according to Smith, A.J.H., Methods in

Enzymology 65: 560-580[1]. On pages 573-575 of Smith, analysis of primer extension products is described, involving treatment of samples with formamide at 100° C and electrophoresis in gels containing urea that are run at elevated temperature. Both of these conditions are known to denature nucleic acid duplexes, and would thus cause separation of an extended primer from its template.

Claim 88 recites a set of reagents comprising a polymerase. Support for this claim is found in the specification on page 9 at lines 18-19 ("They [the primers] must have a free 3' hydroxyl group to allow chain extension by the polymerase") and lines 22-24 ("The chromophore or fluorophore must not interfere with the hybridization or prevent 3'-end extension by the polymerase"). Additional support is found on page 10 at lines 6-9 ("In turn, each tagged primer is then paired with one of the dideoxynucleotides and used in the primed synthesis reaction with the Klenow fragment of DNA polymerase.") and on page 20 at lines 32-34 ("Various fluorescent dye primers have been tested by substituting them for the normal primer in DNA sequence analysis by the enzymatic method.")

Support for the apparatus recited in claims 112-117 is presented on page 6, beginning at line 23 ("This invention also includes a novel system...") through page 7, line 3. Additional support is found beginning on page 12 at line 11 and continuing through page 14, line 18; in Example II on pages 15-16 (particularly page 15 at lines 14-21); page 21 at lines 20-26 ("The separations are again carried out..."); and in Figures 2, 4, 6 and 7.

Various of the new claims recite primers or oligonucleotides that are tagged with chromophores or fluorophores which may be distinguished by their spectral characteristics. Support for these claims is provided in the original claims and in the specification, for example,

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[1] Note that there is a typographical error in the page numbers of this reference in the specification. Applicants have requested herein (see page 2 and the first paragraph of "Remarks" on page 9) that the specification be amended to provide the correct page numbers.

on page 10 at lines 1-3 ("... a set of four fluorophores with different emission spectra, respectively, are used."). A description of the spectra of the fluorophores is provided on page 10 at lines 11-21, and a graphical representation of the spectra is provided in Figure 5.

Therefore, applicants believe that new claims 73-117 are fully supported by the specification as filed, and no new matter has been introduced by these claims.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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